Highly enantioselective construction of the key azetidin-2-ones for the synthesis of carbapenem antibiotics *via* intramolecular C–H insertion reactions of α-methoxycarbonyl-α-diazoacetamides catalysed by chiral dirhodium(II) carboxylates

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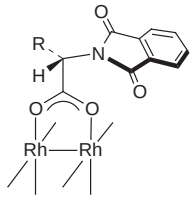
A highly enantioselective construction of 3-oxa-1-azabicyclo[4.2.0]octanes (up to 96% ee) has been achieved by intramolecular C–H insertion of α-methoxycarbonyl-α-diazoacetamides catalysed by dirhodium(II) complexes incorporating *N*-phthaloyl-(*S*)-amino acids as chiral bridging ligands, which provides a new, catalytic asymmetric route to key intermediates for carbapenem antibiotics.

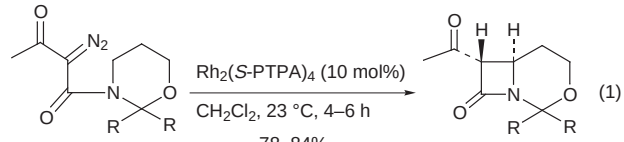
Among a variety of transition metal complexes used to catalyse a broad spectrum of transformations of α-diazo carbonyl



Rh_2(*S*-PTPA)$_4$ R = Bn
Rh_2(*S*-PTA)$_4$ R = Me
Rh_2(*S*-PTV)$_4$ R = Pr^i
Rh_2(*S*-PTPG)$_4$ R = Ph
Rh_2(*S*-PTTL)$_4$ R = Bu^t

compounds, dirhodium(II) complexes have distinguished themselves by their superiority in C–H insertion reactions.[1] Consequently, a great deal of effort is being devoted to the design, synthesis and evaluation of chiral dirhodium(II) catalysts which make it possible to construct both carbocyclic and hetereocyclic systems with high enantioselectivities.[1,2] Our efforts in this area have led to the development of dirhodium(II) carboxylates incorporating *N*-phthaloyl-(*S*)-amino acids as the bridging ligands, which catalyse intramolecular C–H insertion reactions of α-diazo carbonyl compounds to give optically active cyclopentanone and indan-2-one derivatives in high yields and with up to 80 and 98% ee, respectively.[3,4] Herein we report the highly enantioselective construction of 3-oxa-1-azabicyclo-[4.2.0]octanes, which lead to the key azetidin-2-ones for the synthesis of 1-unsubstituted and 1β-methyl carbapenem antibiotics.[5]

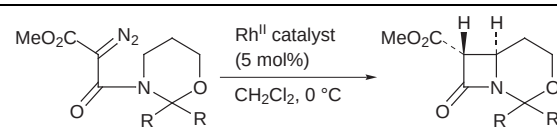
We previously demonstrated that cyclisation of *N*-alkyl-*N*-*tert*-butyl-α-methoxycarbonyl-α-diazoacetamides catalysed by dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-phenylalaninate], Rh_2(*S*-PTPA)$_4$, led to the exclusive formation of azetidin-2-one derivatives of up to 74% ee,[6] wherein installation of a *tert*-butyl group as an *N*-substituent proved to be crucial to enantiocontrol as well as regiocontrol; however, the inability to remove the *tert*-butyl group precluded its application to the synthesis of carbapenem antibiotics. In this respect, of particular interest is the pioneering work of Ponsford and Southgate dating back to 1979.[7] They developed a racemic route to the thienamycin key intermediate *via* the $Rh_2(OAc)_4$-catalysed C–H insertion reaction of α-diazoacetoacetamides **1a** and **1b** tethered to a tetrahydro-1,3-oxazine system. Following the suggestion that the *N*,*O*-acetal moiety could function as a substitute for the *tert*-butyl group, we then examined cyclisation of **1a** and **1b** with the aid of 10 mol% of Rh_2(*S*-PTPA)$_4$. Cyclisation proceeded smoothly to give the 3,4-*trans*-azetidin-2-one derivatives **2a** and **2b**, but we were disappointed to find that there was no asymmetric induction in either case [eqn. (1)].



(1)

Although the steric and electronic differences between the acetyl and methoxycarbonyl groups as the α-substituent of the diazo carbon was thought to be small, we next explored the feasibility of asymmetric induction with α-methoxycarbonyl-α-diazoacetamide **3a**. To our surprise, cyclisation of **3a** under the influence of 5 mol% of Rh_2(*S*-PTPA)$_4$ afforded the 3,4-*trans*-azetidin-2-one derivative **4a** as the sole product in 89% yield and with 90% ee (Table 1, entry 1). While the mechanistic profile is not clear at present, the beneficial effect of the ester group in this system should be underscored.‡ To further enhance the enantioselectivity, we then screened other chiral dirhodium(II) carboxylates, Rh_2(*S*-PTA)$_4$, Rh_2(*S*-PTV)$_4$, Rh_2(*S*-PTPG)$_4$ and Rh_2(*S*-PTTL)$_4$, derived from *N*-phthaloyl-(*S*)-alanine, -valine, -phenylglycine and -*tert*-leucine, respectively. While the catalysis of **3a** provided **4a** with a consistent sense of enantioselection at the insertion site and in more than

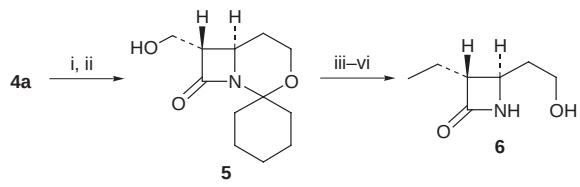
Table 1 Enantioselective C–H insertion reaction of **3** catalysed by chiral Rh^{II} complexes[a]



3a–c **4a–c**

	Substrate				Lactam		
Entry	**3**	R,R	Catalyst	*t*/h	**4**	Yield[b] (%)	Ee[c] (%)
1	**3a**	–(CH$_2$)$_5$–	Rh_2(*S*-PTPA)$_4$	3	**4a**	89	90
2	**3a**	–(CH$_2$)$_5$–	Rh_2(*S*-PTV)$_4$	3	**4a**	86	92
3	**3a**	–(CH$_2$)$_5$–	Rh_2(*S*-PTPG)$_4$	3	**4a**	85	92
4	**3a**	–(CH$_2$)$_5$–	Rh_2(*S*-PTTL)$_4$	4	**4a**	85	93
5	**3a**	–(CH$_2$)$_5$–	Rh_2(*S*-PTA)$_4$	2	**4a**	94	96
6	**3b**	Me,Me	Rh_2(*S*-PTA)$_4$	6	**4b**	89	93
7	**3c**	Et,Et	Rh_2(*S*-PTA)$_4$	8	**4c**	89	83

[a] Reactions were carried out as follows: 5 mol% of the catalyst was added to a stirred solution of the α-diazo amide **3** (1 mmol) in anhydrous CH_2Cl_2 (2 ml) at 0 °C under argon. [b] Isolated yield. [c] Determined by a chiral stationary phase column (Daicel Chiralcel OJ) after reduction with $LiBH_4$ and subsequent benzoylation.

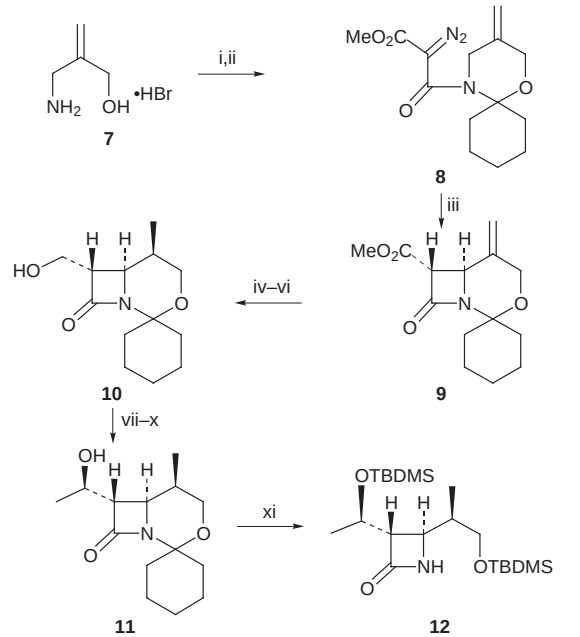


Scheme 1 *Reagents and conditions*: i, $LiBH_4$, THF, 0 °C, 2 h, 94%; ii, recrystallisation from Pr^i_2O–hexane, 90%; iii, Dess–Martin periodinane, CH_2Cl_2, 0 °C, 3 h, 94%; iv, CH_2I_2, Zn, Me_3Al, THF, 0 °C, 2 h, 89%; v, H_2, Pd–C, EtOH, 23 °C, 2 h, 96%; vi, aq. AcOH, 70 °C, 2 h, 97%

92% ee in all cases (entries 2–5), Rh_2(*S*-PTA)$_4$ proved to be the catalyst of choice for displaying the highest degree of enantioselectivity (96% ee, entry 5). With regard to the *N*,*O*-acetal protection, the isopropylidene acetal **3b** exhibited almost the same enantioselectivity as **3a** (entry 6), whereas a dramatic drop in enantioselectivity was observed with the pentylidene acetal **3c** (entry 7). It should be emphasised here that **3a** has distinct advantages over **3b** from the standpoint of its preparative yield.

The azetidin-2-one **4a** {96% ee, $[\alpha]_D^{25}$ +57.7 (*c* 1.02, $CHCl_3$)} thus obtained was then transformed to the key synthetic intermediate **6** for PS-5, which also determined the preferred absolute configuration at the insertion site (Scheme 1). Reduction of **4a** with $LiBH_4$ gave the alcohol **5**, which, upon one recrystallisation from Pr^i_2O–hexane, produced an optically pure sample {mp 89–90 °C, $[\alpha]_D^{25}$ +17.7 (*c* 1.03, $CHCl_3$)}. Oxidation of **5** with the Dess–Martin periodinane followed by sequential methylenation,[8] hydrogenation and hydrolysis afforded the PS-5 intermediate **6** {$[\alpha]_D^{25}$ +25.0 (*c* 1.16, CH_2Cl_2); lit.,[9] +24.3 (*c* 1.33, CH_2Cl_2)}.

Finally, we extended the present protocol to the synthesis of the pivotal intermediate for 1β-methylcarbapenems (Scheme 2).



Scheme 2 *Reagents and conditions*: i, cyclohexanone, $NaHCO_3$, benzene, reflux, azeotropic distillation, 6 h, then methyl malonyl chloride, $PhNMe_2$, CH_2Cl_2, 0 °C, 1 h, 68%; ii, *p*-$AcNHC_6H_4SO_2N_3$, DBU, MeCN, 0 °C, 2 h, 91%; iii, Rh_2(*S*-PTA)$_4$, CH_2Cl_2, 23 °C, 13 h, 83%, 88% ee; iv, $LiBH_4$, THF, 0 °C, 2 h, 91; v, H_2, Raney-Ni (W2), EtOH–EtOAc, 0 °C, 6 h, 96%; vi, recrystallisation from AcOEt–hexane, 82%; vii, Dess–Martin periodinane, CH_2Cl_2, 0 °C, 3 h, 94%; viii, Me_3Al, CH_2Cl_2, 0 °C, 2.5 h, 87%; ix, DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −60 °C, 1 h, 95%; x, K-Selectride®, Et_2O, −20 °C, 2 h, 90%; xi, aq. AcOH, 70 °C, 2 h, then TBDMSCl, imidazole, CH_2Cl_2, 0 °C, 4 h, 94%

Toward this end, α-methoxycarbonyl-α-diazoacetamide **8** bearing an exocyclic olefin was prepared from **7**§ by condensation with cyclohexanone followed by *N*-acylation with methyl malonyl chloride and subsequent diazo transfer. Cyclisation of **8** with the aid of 5 mol% of Rh_2(*S*-PTA)$_4$ proceeded uneventfully to afford the desired azetidin-2-one **9** {$[\alpha]_D^{25}$ +0.90 (*c* 1.05, $CHCl_3$)} in 83% yield and with 88% ee.¶ Reduction of **9** with $LiBH_4$ followed by stereocontrolled hydrogenation[11] furnished the alcohol **10**, which, upon one recrystallisation from AcOEt–hexane, produced an optically pure sample {mp 159–160 °C, $[\alpha]_D^{25}$ +16.9 (*c* 1.06, $CHCl_3$)}. Treatment of **10** with the Dess–Martin periodinane followed by alkylation with Me_3Al,[12] oxidation under standard Swern conditions and stereocontrolled reduction with K-Selectride®[13] produced the alcohol **11**. Hydrolysis and subsequent silylation provided the known intermediate **12** {mp 96–98 °C, $[\alpha]_D^{25}$ −7.93 (*c* 0.98, $CHCl_3$); lit.,[14] −7.88 (*c* 1.03, $CHCl_3$)}. The above transformation also established that the preferred absolute configuration at the insertion site in this cyclisation was the same as that with **4a**, suggesting a common stereochemical reaction course in both series.

The present protocol provides a new, efficient and general method for the catalytic asymmetric synthesis of carbapenems.[15] Further extension of the present method to trinem antibiotics as well as mechanistic and stereochemical studies are currently in progress.

Notes and References

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‡ Reaction of the corresponding α-diazoacetamides in the presence of Rh_2(*S*-PTPA)$_4$ gave a complex mixture of products.

§ Compound **7** was prepared from ethyl α-(bromomethyl)acrylate (ref. 10) in 65% yield by the following sequence: DIBAL-H, CH_2Cl_2, −78 °C, 1 h, then NH_3, MeOH, 23 °C, 6 h.

¶ The enantiomeric purity of **9** was determined by a chiral stationary phase column (Daicel Chiralpak AD) after reduction with $LiBH_4$ and subsequent benzoylation.

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